Pharmacological management of depressive disorders

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Competing interests: Within the last three years (since July 2013) Prof Cleare has served on advisory boards for Livanova and Allergan, and received grant support from Lundbeck.

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Abstract
This article outlines current guidelines for the pharmacological treatment of depression. For acute treatment of moderate to severe depression in the absence of specific factors, the recommendation is treatment with a selective serotonin reuptake inhibitor or mirtazapine. Other options for acute antidepressant treatment are discussed, and advantages and disadvantages of specific drugs are outlined. Recommendations for next-step treatment for patients with an inadequate response include increasing the dose, switching to another antidepressant, augmentation with another agent or using a combination of antidepressants. Again, recommendations for specific drugs are outlined, and the common advantages and disadvantages of specific drugs are listed in a table format. The options for non-pharmacological treatments are briefly explored in regards to symptom severity and other clinical features, and a list of non-pharmacological treatment options is provided.

Keywords
Acute treatment; antidepressant; augmentation; depression; guideline; next-step treatment; recommendation

Key Points

- Correct diagnosis is crucial for the successful management of depression
- Antidepressant medication is recommended as a first-line treatment for moderate to severe or for chronic depression
- In the absence of specific factors, selective serotonin reuptake inhibitors or mirtazapine are recommended for the acute treatment of depression
- Increasing the dose, switching to another antidepressant, augmentation with another agent and a combination of antidepressants are recommended as 'next-step' treatments

Diagnosis

A correct diagnosis of a specific depressive disorder and its severity, chronicity and risk factors is crucial for successful management. Clinicians should have a good working knowledge of diagnostic criteria and be watchful for depressive symptoms in vulnerable groups, but there is no evidence of direct benefit from non-targeted screening.[1]

Most cases can be managed in primary care. Management should include scheduled follow-up with monitoring of symptoms (ideally using standardized outcome measures) and functional recovery, but also focus on adherence to medications. Active case management interventions can be beneficial but are not in widespread use.

Patients should be referred to a psychiatric service if there is a high suicide risk, occurrence of psychotic symptoms or suspicion of bipolar disorder, if there has been insufficient response to treatment and/or if the primary care professional feels insufficiently experienced to manage the case.[2] In addition, all cases involving a child or adolescent presenting with depressive disorder should be referred to the relevant psychiatric services.[3]

Acute treatment and management

Antidepressant medication is a first-line treatment for moderate and severe depression and for any depression continuing for ≥2 years. Antidepressants should also be considered in patients with currently mild depression who have a past history of moderate or severe depression, or where symptoms have persisted for >2–3 months. Antidepressants are not recommended as first-line treatment for mild depressive symptoms of shorter duration unless there is a previous history of recurrent moderate to severe depression.[2] Similarly, pharmacological management is not recommended for children or adolescents with depression unless they suffer from severe symptoms, there has been an insufficient response to alternative treatment and/or there is a past history of recurrent moderate to severe depression.[3]

Psychological therapies are an alternative first-line treatment for mild to moderate depression, and the combination of medication and psychological therapy is recommended in more complicated cases such as chronic, severe, highly recurrent or treatment-resistant depression.[1]

Most antidepressant drugs have broadly similar efficacy, and the choice of specific drug should be based on several factors including the efficacy of drugs on specific symptoms, interaction with other drugs and safety in overdose.[1] In the absence of specific factors, the Maudsley Prescribing Guidelines in Psychiatry[4] recommend a selective serotonin reuptake inhibitor (SSRI) or mirtazapine as first-line treatment because of better tolerability and safety; however, other drugs can be selected based on history of previous responses or specific effects on symptoms (see Table 1 for details on the benefits and disadvantages of specific drugs).

There are few sufficiently powered head-to-head studies directly comparing different antidepressants, but there may be small benefits for escitalopram, sertraline, venlafaxine, mirtazapine, clomipramine and amitriptyline; in more severely ill patients, and in other situations where maximizing efficacy is of overriding importance, these are recommended in preference.[1] Combination treatment with antidepressant and antipsychotic medication (e.g. venlafaxine with quetiapine) is more effective than monotherapy for the treatment of depression with psychotic symptoms. Other factors affecting the choice of antidepressant include:

- patient preference (particularly for medication versus psychological therapy)
- psychiatric and medical co-morbidity, for example using serotonergic antidepressants for co-morbid obsessive-compulsive disorder or generalized anxiety disorder, and tricyclic antidepressants (TCAs) for chronic pain
- interactions with other medications
- previous response to a particular medication
- effects on specific depressive symptoms, such as appetite or sleep
- adverse effects.

The initial phase of acute management should include reviews every 1–2 weeks assessing the response, adherence to treatment, adverse effects and suicide risk. Mild or transient adverse effects (anxiety, nausea with SSRIs) can be managed by psychoeducation. More severe or persistent adverse effects may require a dose reduction, change to an antidepressant with a different adverse effect profile, non-pharmacological management (e.g. diet for weight gain with mirtazapine) or introduction of another medication (short-term benzodiazepines for anxiety, sildenafil or bupropion for sexual dysfunction).[1]

Improvement of symptoms is often first noted during the first 1–2 weeks, and treatment options should be reviewed if there are no signs of improvement after 4 weeks.

Next-step treatment for inadequate response

Before deciding about next-step pharmacological treatment (Table 2), it is important to evaluate and *address other factors* that are possibly contributing to the lack of response.[1] These include assessing adequacy of dose and treatment adherence, and reviewing the diagnosis, including possible psychiatric or medical co-morbidity, but also considering chronic social difficulties involved in maintaining the symptoms. If the review after 4 weeks of adequate treatment shows some improvement, it is recommended to continue treatment for another 2–4 weeks, but proceed with the next-step treatment if there is insufficient improvement at 6–8 weeks.

Next-step drug treatment can consist of *increasing the dose* in the absence of significant adverse effects and if there has been some improvement, particularly with drugs with established dose–response relationships such as venlafaxine, escitalopram and TCAs, and bearing in mind the lack of good evidence for this strategy with other SSRIs.

Another next-step treatment option is *switching to another antidepressant*. This can be initially within the same antidepressant class (SSRIs), but after more than one failure, switching to a different class is recommended. The strongest evidence of improvement is for switching from an SSRI to venlafaxine, but there are also reports of improved remission rates after switching from SSRIs to bupropion, mirtazapine or vortioxetine and agomelatine. In the absence of potentially toxic interactions (i.e. fluoxetine to TCAs or monoamine oxidase inhibitors (MAOIs) to serotonergic drugs) switching or cross-tapering directly without a washout period is recommended.[1]

Further options for next-step treatment are *using add-on therapies* (antidepressant augmentation) or *combining antidepressants*. Augmentation treatments with the strongest evidence are quetiapine, aripiprazole, risperidone (all used in lower doses than for antipsychotic effects) or lithium. The second-line recommendation includes augmentation with olanzapine or tri-iodothyronine, or combination with bupropion, mirtazapine or buspirone. Further recommended options include adding lamotrigine, modafinil or intermittent ketamine infusions.

Relapse prevention and treatment

The goal of treatment should be full remission of symptoms, given the higher rates of relapse associated with persisting residual symptoms. Because of the increased risk of relapse during the 6 months after recovering from depression, the recommendation is to continue the effective treatment for 6–9 months after the symptoms have improved in all patients. For patients with a higher risk of relapse, it is recommended to continue treatment for 1–2 years or even longer given that recurrence rates are 2–3-fold lower on long-term maintenance therapy for as long as it is continued .[1]

If depressive symptoms deteriorate while the patient is on continuation treatment, review the dose and adherence, as well as possible psychiatric and medical co-morbidity and adverse social factors. Where a patient has stopped antidepressant treatment, this should be restarted at the appropriate dose. Patients experiencing a recent relapse despite continued treatment may benefit from support and monitoring even without changing the medication as relapses are often self-limiting. Patients with persisting relapse may require an increased dose of antidepressant or to proceed with next-step treatments in accordance with the guidance above.[1]

Stopping treatment
Abrupt stopping of treatment can result in discontinuation symptoms. Management of these usually mild symptoms should include explanation and reassurance but may require recommencement and slower tapering of the used antidepressant or a switch to fluoxetine.[4]

Other treatment options
A detailed discussion is beyond the scope of this article, but the main options are summarized in Table 3.

Table 1 Examples of advantages and disadvantages of selected antidepressant drugs and their dose range for acute treatment of depression based on the British National Formulary,[5] British Association or Psychopharmacology guidelines[1] and Maudsley Prescribing Guidelines in Psychiatry[4]

Drug	Group	Advantage	Disadvantage
Recommended as first-line treatment			
Sertraline (50–200 mg/day)	SSRI	Most favourable efficacy-to-tolerability profile	Nausea, sexual dysfunction
Escitalopram (10–20 mg/day)			As above + possible QT_c prolongation
Mirtazapine (15–45 mg/day)	Noradrenergic and specific serotonergic antidepressant	Higher response rates than duloxetine, fluoxetine, fluvoxamine and paroxetine	Adverse effect profile includes sedation and weight gain
Further treatment options if suitable in relation to adverse effect profile, previous responses or patient's preference			
Venlafaxine (75–375 mg/day)	SNRI	More effective than SSRIs	Higher drop-out rates due to adverse effects
Clomipramine (30–250 mg/day)	TCAs	Same as or higher efficacy than SSRIs	Less tolerated than SSRIs, higher toxicity in overdose
Imipramine (75–300 mg/day)			
Amitriptyline (75–200 mg/day)			
Phenelzine (45–90 mg/day)	MAOI	More effective for 'atypical depression' (increased appetite/weight gain, increased sleep, severe fatigue) than TCAs	Risk of serious interaction with medications and food
Duloxetine (60 mg/day)	SNRI	More effective than SSRIs for co-morbid pain	Possible lower overall efficacy for depressive symptoms
Agomelatine (25–50 mg/day)	Melatonin (MT1, MT2) agonist and 5HT2C antagonist	Efficacy comparable to SSRIs and venlafaxine	Risk of hepatotoxicity
Vortioxetine (10–20 mg/day)	Serotonin modulator and stimulator	Similar efficacy to SSRI/SNRI medications	Similar tolerability to SSRI/SNRI medications

SNRI, Serotonin-noradrenaline reuptake inhibitor.

Table 2 Next-step drug treatments based on the British Association or Psychopharmacology guidelines[1] and Maudsley Prescribing Guidelines in Psychiatry[4]

	Drug	Advantage	Disadvantage
Switch to another antidepressant			
	Another SSRI	See Table 1	
	Venlafaxine		
	Mirtazapine		
	Vortioxetine		
	Agomelatine		
	Consider TCA or MAOI		
Augmentation or combination			
First line	Quetiapine (150–300 mg/day)	Well tolerated, good evidence	Sedation, weight gain
	Aripiprazole (2.5–10 mg/day)	Well tolerated, good evidence	Akathisia, agitation
	Risperidone (0.5–2 mg/day)	Well tolerated	Hyperprolactinemia, extrapyramidal symptoms
	Lithium (600–1200 mg/day for plasma concentration 0.4–1.0 mmol/litre)	Good evidence	Acute toxicity with narrow therapeutic window, requires plasma level monitoring; thyroid and renal effects
Second line	Olanzapine (2.5–10 mg/day)	Well tolerated	Sedation, weight gain
	Tri-iodothyronine (20–50 microgram/day)	Well tolerated	Requires thyroid function monitoring
	Bupropion (up to 400 mg/day)	Well tolerated	Off licence in UK
	Mirtazapine (30–45 mg/day)	See Table 1	
	Mianserin (30 mg/day)	Well tolerated	Risk of blood dyscrasias
	Buspirone (up to 60 mg/day)	Some evidence	Less well tolerated
Others	Lamotrigine (200–400 mg/day)	Widely used	Risk of rash, requires slow titration
	Modafinil (100–400 mg/day)	Rapid effect	Can worsen anxiety
	Ketamine (0.5 mg/kg intravenously over 40 minutes)	Rapid effect	Not widely available, possible negative cognitive effects, duration of effect unknown, bladder toxicity

Table3 Non-pharmacological treatments of depression based on the British Association or Psychopharmacology guidelines[1] and NICE guideline on depression in adults[4]

Treatment	Advantages	Disadvantages

Psychological therapy	Efficacy of cognitive behavioural therapy, interpersonal therapy and behavioural activation is comparable to antidepressants for mild/moderate depression	Requires active engagement of patients, availability can be variable with local services
ECT	Good efficacy, including for severe and treatment-resistant depression, quicker onset than antidepressants	High relapse rates, cognitive adverse effects (usually temporary)
Repetitive transcranial magnetic stimulation	Reasonable evidence, no major adverse effects	Not widely used, less effective than ECT
Vagus nerve stimulation	Efficacy comparable to pharmacotherapy and psychotherapy in open studies	Invasive procedure, not widely used, lack of evidence from randomized controlled trials
Bright light therapy	Reasonable efficacy for seasonal affective disorder	Limited evidence for non-seasonal depression
Supervised aerobic exercise	Can be effective as adjunct to antidepressants	Not recommended as an alternative to antidepressants

ECT, electroconvulsive therapy.

Key References

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